Journal of Molecular Graphics and Modelling 80 (2018) 224–237

Contents lists available at ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

Conformational and NBO studies of serotonin as a radical scavenger. Changes induced by the OH group

Rosana M. Lobayan*, María Celia Pérez Schmit

Departamento de Física, Facultad de Ciencias Exactas y Naturales y Agrimensura, Universidad Nacional del Nordeste, Avda. Libertad 5300, 3400 Corrientes, Argentina

ARTICLE INFO

Article history:
Received 3 December 2017
Received in revised form 9 January 2018
Accepted 10 January 2018

Keywords:
Serotonin
Atoms in molecules theory
Density functional theory
Ionization potentials
Bond dissociation enthalpies
Molecular electrostatic potential
Natural bond orbital analysis
Conformational search

ABSTRACT

Serotonin (5-hydroxytryptamine, SER) is a neurotransmitter that affects many different processes within the human body. We studied the conformational space of SER, and explored in depth the significant stereoelectronic features for the structure stabilization and antioxidant activity. Forty-eight equilibrium structures were described at the B3LYP/6-311++G(d,p) level, characterizing four non-previously reported conformers. Electron distributions were analyzed by topological QTAIM (Quantum Theory of atoms in molecules) and natural bond orbital (NBO) studies. The study was supplemented by an exploration of molecular electrostatic potential (MEP). Intramolecular hydrogen interactions were also investigated; N10···H—C4 or N10···H—C2 hydrogen bondings were depicted in 5 conformers.

The conformer stabilization and the corresponding energy arrangement were explained by hyperconjugation interactions obtained by NBO analysis. The present study is based on the effect of the 5-OH group on geometric and electronic behavior that we have previously reported on the similar structure tryptamine (TRA). Our interest also lies in SER's free radical scavenging capacity as a member of the indole family. The H-atom abstraction and single-electron transfer mechanisms were taken into account. Our results showed that donor-acceptor interactions play a major role in explaining the changes induced by the OH group, and free-radical scavenging capability of the indole compounds.

1. Introduction

Serotonin (5-hydroxytryptamine, SER) is a neurotransmitter that affects many different processes within the human body [1–5]. Its biological activity is achieved by interacting with more than fifteen different receptors to carry out various functions [1,5]. The flexibility of the ethylamine side chain and 5-OH group was associated with the ability of SER to combine to numerous different receptor sites, thus changing its configuration to fit each receptor; a free radical scavenging activity of SER using electron spin resonance was also demonstrated [6].

Several theoretical conformational studies on SER and other tryptamine derivatives have been previously reported in the literature. Early analysis employed only semiempirical methods. The first *ab initio* calculations accounted for a more expanded conformational search for SER and bufotenin (5-hydroxy-*N*,*N*-dimethyltryptamine) using the SCF method with the STO-3G basis set [7].

At the B3LYP/6-31+G(d) level of theory, twenty-three structures were theoretically characterized [8], linking the findings to previous theoretical and experimental studies on tryptamine (TRA) and 3-indolepropionic acid. Two available configurations for OH group were reported (*anti* and *syn* on the indole N—H group).

Experimentally, eight neutral SER conformers were observed by comparison with the very close structural analog TRA. Ultraviolet and Infrared transitions were assigned, and OH-*syn* and OH-*anti* structures were also distinguished [9].

The knowledge of SER conformers continues to attract the attention of the international scientific community. Recently, the microwave spectrum of SER was observed for the first time [10], a new theoretical study of SER and its hydrated complexes was reported [11], and rotationally resolved electronic spectra together with *ab initio* structural study of SER were also shown [12].

The aim of this work was to carry out a detailed study based on the donor-acceptor interactions of the SER conformational landscape. The structural behavior of conformers was described by characterizing and quantifying the geometric and electron changes induced by the 5-OH group of the indole moiety, taking as reference our previous report on electron distribution of TRA [13].

* Corresponding author.
E-mail address: rlobayan@unne.edu.ar (R.M. Lobayan).

https://doi.org/10.1016/j.jmgm.2018.01.006
1093-3263/

Therefore, the conformational space of SER was scanned, and density functional methods were applied to obtain the lowest energy conformers. To analyze the intramolecular interactions and the features and behavior of the electron distributions, the topological QTAIM (Quantum Theory of atoms in molecules) [14] and natural bond orbital (NBO) [15] frameworks were used. The NBO study on TRA that we had previously reported [13] was also extended. The molecular electrostatic potential was obtained, and further analyzed taking into account the AIM and NBO results. The nature of intramolecular interactions and electron delocalization effects was examined, looking for the side chain involved. The role of the conformational preferences of neurotransmitters was also addressed.

As good key indices for free radical scavenging capability and 5-OH effects, the N—H bond dissociation enthalpies, and adiabatic ionization potentials taking into account the lowest energy SER conformers were computed in gas phase.

The analysis in gas phase has been applied successfully to measure the intrinsic properties, which has been compared to the results of gas phase experiments and will be used to quantify/understand the effects of various solvents on the antioxidant activity of indole derivatives.

2. Methods

A preliminary conformational search was performed taking into account initial molecular dynamic calculations [13,16] by HyperChem modules [17]. The starting conformations obtained were further studied by the density functional theory through Gaussian 03 [18]. Additional structures were found extending the conformational search in a systematic way. Structure optimization procedures were carried out using hybrid and correlation functionals, Becke three-parameter [19], and Lee-Yang-Parr [20], respectively; a scheme identified as the B3LYP method. A 6-311++G (d,p) basis set was employed for all atoms. All studies were performed in gas phase to quantify solvent-free effects. The lowest energy structures were confirmed as stationary points in the hypersurface of the potential energy by a vibrational study, thus obtaining zero-point energy (ZPE) contributions, which were considered in the calculated energy terms.

The study of electron distribution was carried out by analyzing the topology of electron density (ρ) by the QTAIM framework (AIM) [14]. Crucial to the analysis was the characterization of the critical points (CPs) and the curvatures of ρ, and other properties evaluated at the CPs, which constituted a powerful tool to classify a given chemical structure [21,22]. To quantify the net changes introduced by the 5-OH group in these properties, we took into account percent values that included differences of SER conformers with respect to structurally similar TRA conformers:

$$\%\Delta x = \frac{x(SER) - x(TRA)}{x(TRA)} \quad (1)$$

The Natural Bond Orbitals (NBO) framework [23] led to localized orbitals, which can be either bonding (filled or donor) or antibonding (vacant or acceptor) orbitals. The interactions between both bonding and antibonding orbitals were useful as a measure of electron delocalization by the calculation of the second-order stabilization energy ($E^{(2)}$) related to a donor (i), and an acceptor (j). The i/j delocalization was calculated as follows:

$$E^{(2)} = -n_i \frac{F_{ij}^2}{\varepsilon_j - \varepsilon_i} \quad (2)$$

where n_i standed for the population of the donor orbital; F_{ij} is the Fock or Kohn–Sham operator matrix element between orbitals i and j; ε_j and ε_i accounted for the donor and acceptor (i and j NBOs) energies.

The topological analysis was performed with modules of the AIMPAC package [24]. NBO analysis was carried out as implemented within Gaussian 03 package [18].

The study of critical points and bond paths was also performed, and visualized using Multiwfn software [25].

Molecular electrostatic potential (MEP) can be obtained experimentally, and also by computational methods, being useful for analyzing the reactivity of compounds [26–30]. MEP was calculated and analyzed at the van der Waals molecule surface by Gaussian and MOLEKEL 4.0 [31] software.

3. Results and discussion

3.1. Structural and electronic analysis of energy order of conformers

SER (5-hydroxytryptamine) comprises an indole ring, a side chain at position 3 (aminoethyl moiety), and a 5-OH group (Fig. 1). The side chain can assume some distinctive orientations, and the dihedral angles δ_1 (C_2—C_3—C_8—C_9), δ_2 (C_3—C_8—C_9—N_{10}), and δ_3 (C_8—C_9—N_{10}—H_a) [13] can be assigned to different conformers. Another dihedral angle, such as δ_4 (C_4—C_5—O—H), defined the OH arrangement.

Forty-eight minimum energy conformers with C_1 symmetry were found through the conformational landscape in vacuum. Conformers were named according to the values of the four dihedral angles defined above, in the order δ_1, δ_2, δ_3, δ_4, respectively. In energy arrangement the conformers were termed: 1) $A^+G^-G^+C/A^-G^+G^-C$, 2) $A^+G^-G^-C/A^-G^+G^+C$, 3) $A^+G^-G^+T/A^-G^+G^-T$, 4) A^+G^+TC/A^-G^-TC, 5) A^+TG^-C/A^-TG^+C,

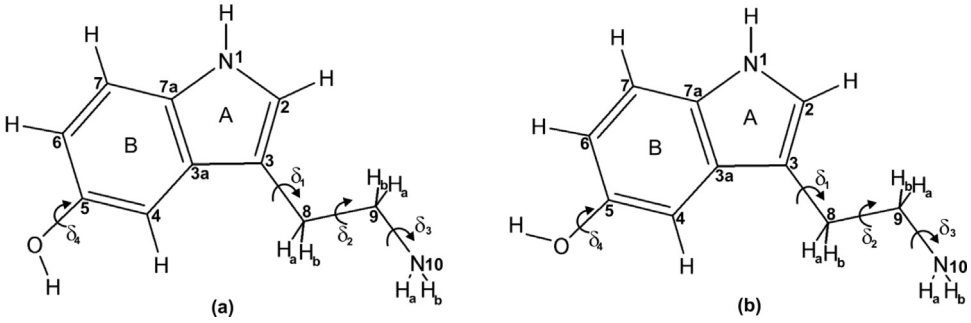

Fig. 1. Planar indole ring, and the aminoethyl side chain of SER backbone. Dihedral angles that define distinct orientations of the aminoethyl side chain, and OH group with respect to ring B are shown. δ_1: C_2—C_3—C_8—C_9, δ_2: C_3—C_8—C_9—N_{10}, δ_3: C_8—C_9—N_{10}—H_a, and δ_4: C_4—C_5—O—H. Type C or OH-*anti* (a) and type T or OH-*syn* (b) conformers are shown.